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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/027,725 | 12/21/2001 | Sabine Flicker | 25401-4 | 9787 |

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| EXAMINER | |
|---|---|
| HUYNH, PHUONG N | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

DATE MAILED: 09/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/027,725 | FLICKER ET AL. | |
| | Examiner | Art Unit | |
| | Phuong Huynh | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *25-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *30,31,36-38,41,45 and 46* is/are allowed.

6)☒ Claim(s) *25-29,32-35,39,40 and 42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 25-46 are pending.

2. Upon reconsideration, the Final Office Action mailed 4/21/06 is hereby withdrawn. A new Office Action is followed.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 34-35 and 44 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a timothy grass Phl p2 pollen allergen specific human IgE Fab comprising a heavy chain consisting of the amino acid sequence as shown in SEQ ID NO: 7, SEQ ID NO: 8 or SEQ ID NO: 9, and a light chain consisting of the amino acid sequence as shown in SEQ I DNO: 10, SEQ ID NO: 11 or SEQ ID NO: 12, respectively for a method of diagnosing type I allergy, a method for environmental allergen detection, and a method for standardization of allergen extract, **does not** reasonably provide enablement for a vaccine against any grass pollen allergy comprising the IgE Fab comprising a heavy chain consisting of the amino acid sequence as shown in SEQ ID NO: 7, SEQ ID NO: 8 or SEQ ID NO: 9, and a light chain consisting of the amino acid sequence as shown in SEQ I DNO: 10, SEQ ID NO: 11 or SEQ ID NO: 12, respectively, or the corresponding complete antibody, a vaccine against any grass pollen allergen comprising the IgE Fab having a heavy chain encoded by the nucleic acid sequence as shown in SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, and a light chain encoded by the nucleic acid sequence as shown in SEQ ID NO: 4, SEQ ID NO: 5 or SEQ ID NO: 6, respectively, and a method for passive immunotherapy of any type I grass pollen allergy as set forth in claim 35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope

of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses the use of Phl p2-specific IgE Fabs and/or whole Ig according to the claimed invention is a vaccine and is for "preventive" purpose. The passive immunotherapy of type I allergy includes preventive or therapeutic purpose, see specification page 4, line 1-3. The specification discloses only three timothy grass pollen Phl p2 allergen specific human IgE Fab fragments consisting of a heavy chain *and* a light chain wherein the heavy chain amino acid sequence consists of SEQ ID NO: 7 and the light chain amino acid sequence consists of SEQ ID NO: 10 or a heavy chain consisting of SEQ ID NO: 8 and a light chain consisting of SEQ ID NO: 11, or a heavy chain consisting of SEQ ID NO: 9 and a light chain consisting of SEQ ID NO: 12, respectively for inhibiting the binding of grass pollen allergic patient's IgE to Phl 2 *in vitro*, (2) An Phlp2 specific antibody comprising the variable region comprising a heavy chain, *and* a light chain of a human IgG1 wherein the variable region comprises a heavy chain amino acid sequence is set forth in SEQ ID NO: 7 and the light chain amino acid sequence is set forth in SEQ ID NO: 10 or a heavy chain is set forth in SEQ ID NO: 8 and a light chain is set forth in SEQ ID NO: 11, or a heavy chain is set forth in SEQ ID NO: 9 and a light chain is set forth in SEQ ID NO: 12 for inhibiting the binding of grass pollen allergic patient's IgE to Phl 2 in vitro, and (3) a diagnostic reagent or a kit comprising said Phl p2 specific human IgE Fabs and/or said specific Phl p2 antibody mentioned above for detection assay (See pages 13 and 17-18). The specification further discloses all three IgE Fabs bound to the same recombinant fragment consisting of the N-terminal 64 amino acids of Phl p2. The specification discloses grafting the variable regions of said Phl p2 specific human IgE Fab fragments onto human IgG1 (page 3) for suppressing Phl p2 degranulation of basophiles. The specification discloses the claimed the recombinant phl p2-specific IgE Fabs *may be* useful for induction of a protective mucosal immunity (see page 16). The specification at page 14 discloses IgE Fabs inhibit the binding of allergic patient's IgE to rPhl p2 in vitro.

However, the specification does not teach *in vitro* data correlated with *in vivo prevention* of any grass pollen allergy in humans. The specification does not teach how to *prevent* any grass pollen allergy using any of Phl p-2 specific IgE-Fabs and/or whole Ig mentioned above. The

intended use of a "vaccine" is for *preventive* purpose, see page 4, lines 1-3. Claim 35 is included in this rejection because passive immunotherapy of type I allergy includes *preventive* or therapeutic purpose, see specification page 4, line 1-3. There is a lack of in vivo working example demonstrating that the claimed IgE Fab antibody or the whole corresponding Ig, i.e. IgE is effective as a vaccine to prevent any grass pollen allergy. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions for an in vitro assay does not permit a single extrapolation of vitro assays to human prevention of type I allergy with any reasonable degree of predictability.

Freshney et al, of record, teach culture environment lacks the several systemic components involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro than in vivo, but may not be truly representative of the tissue fro which the cells were derived (see enclosed pages in Culture of Animal Cells, in particular).

Denepoux et al, of record, teach various recombinant human monoclonal antibody Fabs to birch pollen allergen Bet v1 such as rBAB2 cannot interfere with allergic effector cells, mast cells, and basophils because they lack Fc region. However, this antibody whose binding to its allergen further enhances the binding of anaphylactic IgE and thus contributes to disease aggravation rather than reduce allergen-induced allergic reaction (see page 46, col. 1, abstract, in particular).

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/21/06 have been fully considered but are not found persuasive.

Applicants' position is that Phl p2 is defined as grass pollen specific IgE-Fabs. Studies described at pages 5-16 involved grass pollen allergic patient's IgE antibodies and indicate that the Phl p2-specific IgE Fabs (grass pollen specific IgE-Fabs) have therapeutic potential, for example, building of the stable defense line against intruding allergens and/or inducing a protective mucosal immunity.

In response, the specification at page 13-16 discloses IgE Fabs inhibit the binding of allergic patient's IgE to rPhl p2 **in vitro**. The specification at page 4 lines 1-3 discloses the use of Phl p2-specific IgE Fabs and/or whole Ig and the vaccine is "preventive" or for passive immunotherapy of type I allergy. However, the specification does not teach in vitro data correlated with *in vivo* **prevention** of grass pollen allergy in humans. The specification does not teach how to prevent any grass pollen allergy using any Phl p-2 specific IgE-Fabs and/or whole Ig mentioned above. Accordingly, undue experimentation would be required for one skill in the art to practice the claimed invention.

5. Claims 25-29, 32-34, 39-40 and 42-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any grass pollen group 2 allergen specific human IgE Fab having any *combination* of a heavy chain consisting of the amino acid sequence as shown in SEQ ID NO: 7, SEQ ID NO: 8 or SEQ ID NO: 9, and a light chain consisting of the amino acid sequence as shown in SEQ ID NO: 10, SEQ ID NO: 11 or SEQ ID NO: 12 as set forth in claim 25, (2) any isolated grass pollen group 2 allergen specific antibody comprising any *human IgG* and the variable regions of the IgE Fab of claim 45 as set forth in claims 26 and 40, and (3) any "corresponding complete antibody" as set forth in claims 32, 34, 42 and 44.

The specification discloses only three clones, i.e. 60, 94 and 100 of timothy grass pollen Phl p2 allergen specific human IgE Fab fragments via combinatorial library approach. The three clones of Phl p2 specific IgE-Fab consisting of a heavy chain *and* a light chain wherein the heavy chain amino acid sequence consists of SEQ ID NO: 7 and the light chain amino acid sequence consists of SEQ ID NO: 10 or a heavy chain consisting of SEQ ID NO: 8 and a light chain consisting of SEQ ID NO: 11, or a heavy chain consisting of SEQ ID NO: 9 and a light chain

consisting of SEQ ID NO: 12, respectively for inhibiting the binding of grass pollen allergic patient's IgE to Phl 2 *in vitro*. The specification discloses "we have no proof that exactly those heavy chain and light chain combinations which we isolated via the combinatorial library approach existed in the allergic patient for construction of the library", see page 15. The specification further discloses the whole Ig molecules comprising grafted variable regions of any one of the IgE Fabs mentioned above onto human IgG1 (see page 3, lines 7-12).

With the exception of the specific clones comprising the specific combination of heavy and light chain as set forth in claims 45 and 46, there is insufficient written description about any grass pollen group 2 allergen specific human IgE Fabs having *any* combination of heavy and light chain, such as a heavy chain amino acid sequence consists of SEQ ID NO: 7 and a light chain amino acid sequence consisting of SEQ ID NO: 11, or a human IgE Fab having a heavy chain amino acid sequence consists of SEQ ID NO: 7 and a light chain amino acid sequence consisting of SEQ ID NO: 12, or a human IgE Fab having a heavy chain amino acid sequence consists of SEQ ID NO: 8 and a light chain amino acid sequence consisting of SEQ ID NO: 10, or a human IgE Fab having a heavy chain amino acid sequence consists of SEQ ID NO: 8 and a light chain amino acid sequence consisting of SEQ ID NO: 12, or a human IgE Fab having a heavy chain amino acid sequence consists of SEQ ID NO: 9 and a light chain amino acid sequence consisting of SEQ ID NO: 10 or a human IgE Fab having a heavy chain amino acid sequence consists of SEQ ID NO: 9 and a light chain amino acid sequence consisting of SEQ ID NO: 12 or the corresponding nucleic acid encoding such antibodies (claims 39).

With regard to "the corresponding complete antibody" as set forth in claims 32 and 42, it is not clear what is meant by the corresponding complete antibody. The specification discloses group 2 allergen specific human IgE Fabs from either clone 60, 94 or 100 grafted onto only human IgG1 (see specification page 3, lines 7-12). The specification does not describe the complete IgE, for example.

With regard to "an isolated grass pollen group 2 allergen specific antibody comprising any *human IgG* and the variable regions of the specific human IgE Fabs as set forth in claims 26 and 40, the specification discloses group 2 allergen specific human IgE Fabs grafted onto only human IgG1 (see specification page 3, lines 7-12). The specification does not describe variable regions of the IgE Fab of claim 45 grafted onto any other human IgG subtype such as IgG2, IgG3, IgG4 and the corresponding nucleic acid encoding such antibody.

The specification discloses only three Phl p2-specific human IgE Fabs and whole Ig comprising the variable regions of the IgE Fabs from clone 60, 94 or 100 grafted onto human IgG1, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of a *complete* grass pollen group 2 allergen specific human IgE and any isolated grass pollen group 2 allergen specific antibody comprising any human IgG and the variable regions of the IgE Fab as claimed as well as any grass pollen group 2 allergen specific human IgE Fab comprising any combination of heavy and light chain as set forth in claim 25. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. Claims 26 and 40 are rejected under 35 U.S.C. 1 12, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The term "human *IgG*" in claims 26 and 40 represents a departure from the specification and the claims as originally filed. The specification discloses group 2 allergen specific human IgE Fabs from clone 60, 94 or 100 grafted onto only human **IgG1**. The specification does not describe variable regions of the IgE Fab of claim 45 grafted onto any other human IgG subtype such as IgG2, IgG3, IgG4 and the corresponding nucleic acid encoding such antibody.

7. Claims 30, 31, 36-38, 41, 45 and 46 are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

9. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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